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RESEARCH ARTICLE

ADUCANUMAB: A PROMISING MONOCLONAL ANTIBODY FOR ALZHEIMER'S DISEASE

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ABSTRACT

Aducanumab is a novel humanized monoclonal antibody that targets mainly Aβ amyloid plaque and hyperphosphorylated tau proteins. Recently, this drug gets accelerated FDA approval for mild to moderate Alzheimer's disease but it did not get EMA approval. There have been numerous discussions surrounding the approval of this medicine without a confirmed clinically meaningful benefit.Aducanumab's pharmacokinetics and pharmacodynamic properties, data from the drug's efficacy and safety trials, the consequences of the drug's controversial approval, and the future paths in the therapy of AD patients are all outlined in this narrative review.In this narrative review, total 10 clinical trials are included and these studies show high doses of Aducanumab infusion show modest improvement in delaying the disease process but can't reverse it. Despite the criticism, Aducanumab had an impact on downstream tau pathology, which may pave the way for an AD combination therapy strategy (anti-tau and anti-amyloid drug).

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INTRODUCTION

A clinical syndrome known as dementia is characterized by a progressive decline in two or more cognitive functions, such as memory and behavior, which results in a loss of the ability to carry out instrumental and/or fundamental daily activities. Up to 80% of dementia diagnoses are due to Alzheimer's disease (AD), a neurodegenerative disease[1]. The two main causes of this neurodegenerative disease process are the accumulation of amyloid plaques and neurofibrillary tangles (NFTs) of hyperphosphorylated tau[1]. Additional contributing causes include the loss of neurons, gliosis, genetic abnormalities, cerebrovascular amyloidosis, and decreased levels of neurotransmitters[2]. The results of autopsies for AD show that there has been a significant loss of neurons, as seen by the cortical volume shrinking, up to a 50% drop in gyri size, and an increase in sulci size[3]. Although the number of Alzheimer's patients is increasing day by day, we have no definitive treatment options for curing this disease rather than decreasing the symptoms[4]. The few treatment options available for Alzheimer's disease are Memantamine, Recently, a drug named Aducanumab was approved by FDA for Alzheimer's disease which targets the pathogenetic pathway of aggregation of beta-amyloid plaque. The company, Neurimmune first manufactured this monoclonal antibody in 2007 and later on the license was sold to Biogen. The FDA issued conditional expedited approval on June 7, 2021. Being the initial disease-modifying medication, Aducanumab targets the soluble and insoluble aggregates of amyloid[5]. The amyloid-beta pathway has been the focus of the majority of pharmacological interventions so far; however, anti-Amyloid antibody clinical outcomes have been ineffective and unable to achieve their intended goals[6]. Higher doses of Aducanumab have been proven to have a minimal effect on patients' cognitive impairment in the early stages of Alzheimer's dementia[7]. Even though the majority of the U.S. FDA advisory board members opposed the drug's approval, conditional approval was therefore given subject to the completion of future investigations. Although the majority of patient welcomes the possibility of an exciting new AD medication, the approval of Aducanumab adds needless uncertainty for patients, doctors, and researchers. In Australia, Brazil, and Japan, the medication is being evaluated[8]. So, in this narrative review, we provide an

overview of Aducanumab's pharmacological aspect, and its development, discuss the available trial data, and its approval, and the future aspect of the treatment of Alzheimer's disease.

Literature search: The literature search was done from inception to till on 25th July, 2023.Information was gathered by utilizing the US FDA website, Pub med, Google Scholar, MEDLINE, Manufacturer's website, and Clinicaltrial.gov. The search keywords are Alzheimer's disease, Aducanumab, Mechanism of action, approval, cost, clinical trials etc.

Pharmacology

Structure of Aducanumab: The chemical structure of this drug is $C_{6472}H_{10028}N_{1740}O_{2}0_{14}S_{46}$ and its molar mass is 45912.34 $g \cdot mol^{-1}$ [9]

Pharmacokinetic study: A population PK study was used to describe the pharmacokinetics (PK) of Aducanumab utilizing concentration data from 2961 Alzheimer's disease patients who received Aducanumab in single or multiple doses [10]. The systemic accumulation of Aducanumab was 1.7-fold and required 16 weeks of repeated dosing with an every 4-week regimen to attain steady-state concentrations. At the dose range of 1 to 10mg/kg per 4 Weeks, Aducanumab's maximum concentration (Cmax), minimum concentration (Cmin), and area under steady-state plasma concentration versus time curve (AUCss) all increased proportionately[10]. Volume of distribution in steady state has a mean value (95% CI) of 9.63 L (9.48, 9.79). Aducanumab is anticipated to be broken down into tiny peptides and amino acids via catabolic processes. The clearance (95% CI) for Aducanumab is 0.0159 L/hr. and the terminal half-life is 24.8 days[10].

Pharmacodynamic study

Mechanism of action

Amyloid hypothesis and Aducanumab: The pathogenesis of the leading cause of dementia, Alzheimer's is very complex and multifactorial[11]. Among them, aggregation of Aβ amyloid protein extracellularly and accumulation of neurofibrillary tangles (hyperphosphorylated tau proteins) intracellularly are two main causes[12]. When Amyloid precursor protein (APP) starts to cleave abnormally by β-secretase and γ-secretase, it results in the formation of insoluble Aβ fibrils. Following this, Aβ oligomerizes, diffuses into synaptic clefts and disrupts synaptic signaling[13]. It then polymerizes into immobile amyloid fibrils that clump together to form plaques. The microtubule-associated protein is hyperphosphorylated as a result of this polymerization, which causes it to polymerize into insoluble NFTs. Figure 1 shows the amyloidogenic pathway.

Following the formation of plaques and tangles, the microglia around the plaques are recruited. This contributes to neurotoxicity by promoting microglial activation and local inflammatory response[14]. Aducanumab belongs to a new generation of monoclonal antibodies that target Aβ aggregates selectively[15]. Fully human IgG1 monoclonal antibody Aducanumab works by dissolving these amyloid clumps into more manageable oligopeptides or amino acids[16]. Aducanumab has higher selectivity to parenchymal amyloid than vascular amyloid[17].

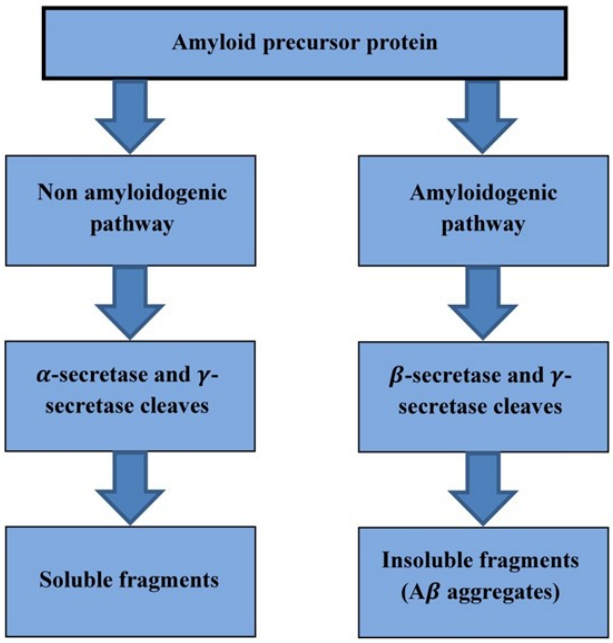

Figure 1. Amyloidogenic pathway for Alzheimer's disease

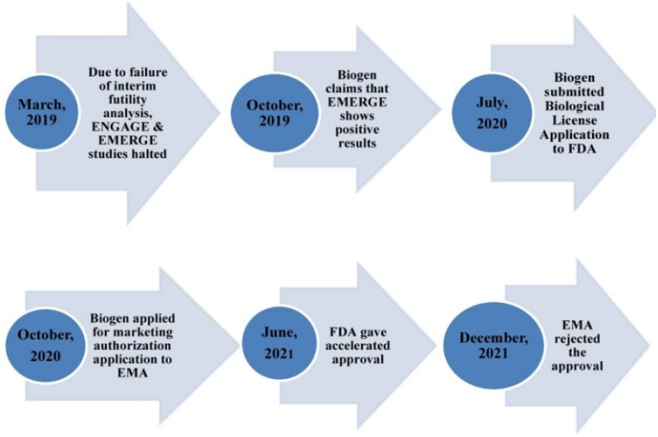

Figure 2. Events occurred for approval of Aducanumab

Tau proteins and Aducanumab: Besides Aβ amyloid, tau proteins play an important role in Alzheimer's disease. Due to the significant neurotoxic effects of the tau protein, tau aggregation is crucial in the emergence of clinical Alzheimer's disease within the complicated pathological interplay of amyloid, tau, neuroinflammation, and other variables. Neurofibrillary tangles (NFTs) are a representation of Alzheimer disease's second defining feature. They are made up of linked helical filaments that are produced as a result of tau hyperphosphorylation in the neuronal cell body. The stabilization of microtubules and vesicular transport is typically accomplished by the Tau protein[18]. In physiological situations, the Tau protein is perfectly balanced between the phosphorylated and dephosphorylated states. Nevertheless, in pathological conditions, excessive phosphorylation produces NFT production, which is responsible for the instability and death of neurons[19]. In the initiation of the pathogenic process, phosphorylated-Tau protein (p-Tau) can also build up in the dendritic spines, altering postsynaptic transmission. p-Tau can propagate trans-synoptically between associated neurons and cause the development of AD[20]. Aducanumab was claimed to have an effect on the second hallmark of Alzheimer's disease, the phosphorylated-Tau level, which is evaluated in CSF and by positron emission tomography (PET) [19].

Table 1. Baseline disease characteristics in emerge and engage study [25].

	EMERGE			ENGAGE		
	PLACEBO (n=548)	LOW DOSE (n=543)	HIGH DOSE (n=547)	PLACEBO (n=545)	LOW DOSE (n=547)	HIGH DOSE (N=555)
1.RBANS delayed memory score, mean ± SD	60.5±14.23	60.0±14.02	60.7±14.15	60.0±13.65	59.5±14.16	60.6±14.09
2.MMSE score, mean ± SD	26.4±1.78	26.3±1.72	26.3±1.68	26.4±1.73	26.4±1.78	26.4±1.77
3.CDR global score, n (%) 0.5 1	 544 (99.3) 3 (0.5)	 534 (100) 0	 546 (99.8) 1(0.2)	 544(99.8) 1(0.2)	 546(99.8) 1(0.2)	 554 (99.8) 0
4.CDR-SB score, mean ±SD	2.47±0.999	2.46±1.011	2.51±1.053	2.40±1.012	2.43±1.014	2.40±1.009
5.ADAS-cog 13 score, mean ± SD	21.9±6.73	22.5±6.76	22.2±7.08	22.5±6.56	22.5±6.30	22.4±6.54
6.ADCS-ADL-MCI Score, mean± SD	42.6±5.73	42.8±5.48	42.5±5.82	43.0±5.55	42.9±5.73	42.9±5.70

Table 2. Efficacy data from EMERGE Study and ENGAGE Study (78 week) [23]

	EMERGE Study			ENGAGE Study		
		Difference vs Placebo (%) p-value			Difference vs Placebo (%) p-value	
	Placebo decline (N=548)	Low dose (N=543)	High dose (N=547)	Placebo decline (N=545)	LOW dose (N=547)	High dose (N=555)
1.CDR-SB	n=288 1.74	n=290 -0.26(-15%) 0.0901	n=299 -0.39(-22%) 0.0120	n=333 1.56	n=331 -0.18(-12%) 0.2250	n=295 0.03(2%) 0.8330
2.MMSE	n=288 -3.3	n=293 -0.1 (3%) 0.7578	N=299 0.6(-18%) 0.0493	n=332 -3.5	n=334 0.2(-6%) 0.4795	n=297 -0.1(3%) 0.8106
3.ADAS-Cog13	n=287 5.162	N=289 -0.701(-14%) 0.1962	N=293 -1.400(-27%) 0.0097	n=331 5.140	n=332 -0.583(-11%) 0.2536	n=294 -0.588 (-11%) 0.2578
4.ADCS-ADL-MCI	n=283 -4.3	n=286 0.7(-16%) 0.1515	n=295 1.79(-40%) 0.0006	n=331 -3.8	n=330 0.7(-18%) 0.1225	n=298 0.7(-18%) 0.1506
5.NPI-10	n=282 1.5	n=283 -0.5(-33%) 0.3921	N=291 -1.3(-87%) 0.0215			

Table 3. Biomarkers and CSF analyte changes in EMERGE Study[23, 24]

		Difference vs Placebo (P-Value)	
	Placebo change from baseline	LOW DOSE	HIGH DOSE
Amyloid PET	n=93 0.014	n=100 -0.179 p<0.0001	n=109 -0.278 p<0.0001
CSF ANALYTE			
β-amyloid CSF	n=28 -30.69	n= 33 179.57, p<0.0001	n=17 318.88, p<0.0001
p-Tau CSF	n=28 -0.49	n=33 −15.64, p=0.0035	n=17 −22.44, p=0.0005
t-Tau CSF	n=28 -0.39	n=33 −86.74, p=0.0148	n=17 −112.05, p=0.0008

Table 4. Tau PET changes from baseline to week 78 [23- 25]

Tau PET Composite Region	**Change in placebo**	**Difference of ADUCANUMAB versus Placebo(78 week)**	
		Low Dose	High Dose
Frontal	n=12 0.090	n=14 −0.049 p=0.0876	n=11 −0.073 p=0.0212
Medial Temporal	n=12 0.082	n=14 −0.115 p=0.0012	n=11 −0.132 p=0.0005
Temporal	n=12 0.082	n=14 −0.065 p=0.1174	n=11 −0.096 p=0.0304

Table 5. Summary of safety [25].

	EMERGE			ENGAGE		
	Placebo (n=547)	Low dose (n=544)	High dose (n=547)	Placebo (n=541)	Low dose (n=548)	High dose (n=558)
1.Patients with any event, n (%)	476 (87.0)	477 (87.7)	505 (92.3)	465 (86.0)	491 (89.6)	500 (89.6)
2.ARIA-E (%)	12 (2.2)	140 (25.7)	86 (34.0)	16 (3.0)	139 (25.4)	198 (35.5)
3.Headache (%)	83 (15.2)	106 (19.5)	106 (19.4)	81 (15.0)	98 (17.9)	114 (20.4)
4.ARIA-H ,microhemorrhage (%)	38 (6.9)	88 (16.2)	102 (18.6)	31 (5.7)	85 (15.5)	98 (17.6)
5.Nasopharyngitis (%)	90 (16.5)	70 (12.9)	87 (15.9)	67 (12.4)	64 (11.7)	66 (11.8)
6.ARIA-H, superficial siderosis (%)	14 (2.6)	50 (9.2)	73 (13.3)	10 (1.8)	48 (8.8)	86 (15.4)
7.Fall (%)	68 (12.4)	64 (11.8)	69 (12.6)	55 (10.2)	77 (14.1)	83 (14.9)

Table 6. Adverse events that had an incident rate greater than 10% [25]

	EMERGE			ENGAGE		
	Placebo (n=547)	Low dose (n=544)	High dose (n=547)	Placebo (n=541)	Low dose (n=548)	High dose (n=558)
1.Patients with an AE, n (%)	476 (87.0)	477 (87.7)	505 (92.3)	465 (86.0)	491 (89.6)	500 (89.6)
2.Patients with an SAE, n(%)	77 (14.1)	69 (12.7)	66 (12.1)	69 (12.8)	71 (13.0)	71 (12.7)
3.Patients permanently discontinuing treatment due to AE, n(%)	16 (2.9)	42 (7.7)	48 (8.8)	28 (5.2)	45 (8.2)	64 (11.5)
4.Patients permanently discontinuing treatment due to ARIA, n (%)	1 (0.2)	25 (4.6)	36 (6.6)	6 (1.1)	27 (4.9)	41 (7.3)
5.Number of all-cause deaths, n (%)	5 (0.9)	0	6 (1.1)	0	3 (0.5)	2 (0.4)

Studies show Efficacy and Safety

Efficacy: The two main studies were conducted to know the efficacy and safety of a new drug named "Aducanumab". Results from Biogen's presentation at the Clinical Trials on Alzheimer's Disease conference (CTAD) in December 2019 and the FDA and Biogen briefing document that was produced following the Peripheral and Central Nervous System Drugs (PCNS) Medications Advisory Committee meeting were used to create the results displayed below. The ENGAGE (1647 patients) and EMERGE (1638 patients) trials were identically designed to assess Aducanumab's safety and efficacy in mild cognitive impairment version (MCI) and mild Alzheimer's disease patients [21, 22]. Participants were assigned a placebo, low dose, high dose in a 1:1:1 ratio. Aducanumab is available in two dose regimens: low-dose (3 and 6 mg/kg for ApoE4 carriers and non-carriers, respectively) and high-dose (6 and 10 mg/kg for ApoE4 carriers and non-carriers, respectively) [23, 24].

Dosing Strategy[23]

Dosing Protocol Versions 1-3

- Low dose: −
- ApoE4 carriers: 3 mg/kg after titration over 8 weeks
- ApoE4 non carriers: 6 mg/kg after titration over 24 weeks
- High dose: −
- ApoE4 carriers: 6 mg/kg after titration over 24 weeks
- ApoE4 non carriers: 10 mg/kg after titration over 24 weeks

Dosing Protocol Versions 4-6

- Low dose: − Unchanged
-
- High dose: − 10 mg/kg (after titration over 24 weeks) in all participants regardless of the participant's ApoE4 Status.

These studies' major goal was to determine how well Aducanumab prevented cognitive deterioration. Four well-known clinical efficacy scales were employed by Biogen to analyze it. The Clinical Dementia Rating-Sum of Boxes (CDR-SB) change from baseline to week 78 was the primary outcome. The Mini-Mental State Examination (MMSE), the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13) and the Alzheimer's disease Cooperative Study-Activities of Daily Life Inventory-Mild Cognitive Impairment (ADCS-ADL MCI) version all have secondary goals of evaluation. Additionally, sub studies were carried out to examine the changes in tau PET, amyloid PET, and CSF (cerebrospinal fluid) indicators such phosphorylated tau (p-Tau), total tau (t-Tau), and the 42-amino type of amyloid [23, 24].**Table 1** shows baseline disease characteristics in EMERGE and ENGAGE study and efficacy data from EMERGE Study and ENGAGE Study (78 week) seen in Table 2.

Biomarkers and radiological study: The following biomarkers were evaluated in both studies: (1) Assessment of the brain's amyloid pathology utilizing 18F-florbetapir PET and cerebrospinal fluid (CSF) A1-42 levels (2) Tau pathology as evaluated by 18F-MK-6240 Tau; (3) change in brain volume as examined by MRI; and (4) intracellular tau accumulation as assessed by CSF p-Tau levels and neurodegeneration as assessed by CSF t-Tau levels. Several clinical evaluations were carried out at the baseline, six months, one year, and eighteen months. A PET scan for amyloid was finished at six and eighteen months.

Table 7. Summary of clinical trials of Aducanumab

Trial name (NCT number)	Study center	Study design	Phase	Sample size	Groups		Primary outcome	Secondary outcome	Conclusion
					Control	Intervention			
1.PRIME NCT01677572 [29]	U.S.A. (32 sites).	Randomized Clinical Trial (RCT), Placebo-Controlled, Double-Blinded, Multiple Dose Study	Phase1	197 participants	Placebo	Aducanumab (1, 3, 6, and 10mg/kg)	Number of Participants with Adverse Events	a)Change from baseline in florbetapir-fluorine-positron (18F-AV-45F-AV-45)emission tomography (PET) imaging b)Multiple dose pharmacokinetic (PK): serum concentrations of Aducanumab c)Change from Baseline in Incidence of Anti-Aducanumab Antibodies in Serum	Analysis of 165 patients' PET scans revealed dose- and duration-dependent results.
2.. NCT01397539 [30]	U.S.A. (3 Sites).	Randomized, Blinded, Placebo-Controlled,Ascending Dose Study	Phase1	53 participants	Placebo	Aducanumab 0.03,1,3 ,10, 20, 30, and 60 mg/kg	Number of Participants with Adverse Events as a Measure of Safety and Tolerability	a)Area Under the Curve from Time Zero Extrapolated to Infinity (AUC0-INF) b)Area Under the Curve from Time Zero to Time of the Last Measurable (AUC0–t) c)Concentration : Maximum Concentration [Cmax] of BIIB037 d)Time to Cmax [Tmax] e)Elimination Half-life [t1/2] f)Clearance [Cl] g)Incidence of Anti-BIIB037 Antibodies in Serum	The safety and tolerability profile of Aducanumab is acceptable.
3. NCT02782975 [31]	USA (2 Sites).	Randomized, Open-Label, Parallel-Arm Study	Phase1	28 healthy participants	No	Aducanumab (Subcutaneous) Aducanumab (Intravenous)	a) PK parameter of SC dose, IV dose of aducanumab: Absolute Bioavailability, AUC0-INF, Cmax, Tmax	a) Number of participants experiencing Adverse Events (AEs) and Serious Adverse Events (SAEs), with clinically significant vital sign abnormalities, with clinically significant laboratory assessment abnormalities, with clinically significant 12-lead electrocardiograms (ECGs) abnormalities b)PK parameter of aducanumab: AUC0–t, t1/2, Volume of distribution (Vd), Apparent total body clearance (CL/F)	No results are posted
4. PROPEL NCT02434718 [32]	Japan (7 sites).	Randomized, Double-Blind, Placebo-Controlled study	Phase 1	21 patients	Placebo	Aducanumab	a) Incidence and nature of adverse events / serious adverse events b) Clinically significant changes in vital signs and 12-lead electrocardiogram (ECG) data; abnormalities in neurological and physical examinations c)Brain magnetic resonance imaging (MRI) findings to assess amyloid-related imaging abnormalities (ARIA), including incidence of ARIA-E (edema) or ARIA-H (hemosiderosis)	AUC0-INF, AUC0–t, Cmax, Tmax, t1/2, Volume of distribution at steady state(Vss), Clearance (CL) after a single IV infusion ofaducanumab, Incidence of anti-aducanumab antibodies in serum	No results are available.

Continue ….

5. NCT04924140 [33]	USA (2 Sites).	Randomized, Open-Label, Parallel-Arm Study	Phase1	30 healthy participants	No	Aducanumab (Intravenous) Aducanumab (Subcutaneous)	a) Area Under the Concentration-Time Curve from Time 0 to Infinity (AUCinf) of Aducanumab b)Maximum Observed Concentration (Cmax) of Aducanumab	a) Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs),Clinically Significant Abnormalities in Vital Signs,Clinically Significant Abnormalities in 12-Lead Electrocardiograms (ECGs),Clinically Significant Abnormalities in Laboratory Assessments b)AUC0–t, Cmax, Tmax, t1/2, Volume of Distribution (Vd) or Apparent Volume of Distribution (V/F), Clearance (CL) or Apparent Clearance (CL/F)	No results are posted.
6.EVOLVE NCT03639987 [34]	USA (22 Sites).	Multicenter, Randomized, Parallel-Group, Double-Blind	Phase2	52patients.	Placebo	Aducanumab	Number of Participants With Clinically Impactful Amyloid-related Imaging Abnormalities	a)Number of Participants With ARIA by Severity as Obtained on Magnetic Resonance Imaging, With Symptomatic ARIA by Severity, Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs), With Aducanumab Concentration in Serum , With Antiaducanumab Antibodies in Serum b)Time to Onset of ARIA as Obtained on MRI,Time to Resolution of ARIA as Obtained on MRI,Time to Onset of Symptomatic ARIA c)Change From Baseline in the Montreal Cognitive Assessment	The study is halted after an assessment of the futility of the ENGAGE and EMERGE trials
7. ENGAGE NCT02477800 [21]	181 sites (U.S.A., France, Australia, Spain, Austria, Canada, Denmark, U.K., Germany, Italy, Japan, Korea, Portugal, and Taiwan)	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study	Phase3	1647 patients	Placebo	Aducanumab (High dose, Low dose).	Change From Baseline in Clinical Dementia Rating Sum of Boxes (CDR-SB) Score	a)Change From Baseline: Mini-Mental State Examination (MMSE) Score, Alzheimer's Disease Assessment Scale-Cognitive Subscale(ADAS-Cog 13) Score, Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment Version) (ADCS-ADL-MCI)	Terminated due to anticipated lack of advantage.
8. EMERGE NCT02484547 [22]	180 sites (Belgium, Italy, Canada, Finland, France, Sweden, Germany, Japan, Poland, Spain, Switzerland, Netherlands, and U.S.A.)	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group	Phase 3	1643 participants	Placebo	Aducanumab	Change From Baseline in Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB) Score	Change From Baseline: Mini Mental State Examination (MMSE) Score, Alzheimer's Disease Assessment Scale-Cognitive Subscle, Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory	High-dose aducanumab reduced clinical decline
9. EMBARK NCT04241068 [35]	229 sites (Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, Korea, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, Taiwan, U.K., and U.S.A.)	Open-Label,Randomized Multicenter, Safety Study	phase IIIb (24-month)	1696 participants	No	Aducanumab (Titretedupto 10 mg/kg)		Core Treatment Period: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs), Number of Participants with AEs Leading to Treatment Discontinuation or Study Withdrawal, Number of Participants with Amyloid-related Imaging Abnormality-Edema (ARIA-E), Number of Participants with Amyloid-related Imaging Abnormality- Hemorrhage or Superficial Siderosis (ARIA-H), Number of articipants With Antidrug Antibodies (ADAs) in Serum	Estimated study completion date is February 24, 2025
10. ADUHELMICARE NCT Pending [36]	200 sites in USA	Observational prospective, multicenter, noninterventional real-world study	phase IV	Expected 6000 participants	No	Aducanumab			Confirmatory phase IV trial design is still in progress, and up to five years of participant monitoring is planned.

Table 8. Dosing schedule of Aducanumab

IV INFUSION (Every four weeks)	ADUHELM Dosage (Given for approximately 1 hour)
Infusions one and two	One mg/kg
Infusions three and four	Three mg/kg
Infusions five and six	Six mg/kg
Infusions seven and beyond	Ten mg/kg

While brain MRI images were performed at 6 months and 18 months, the CSF and tau PET evaluations were obtained at 18 months [24, 25].Biomarkers and CSF analyte changes in EMERGE study seen in Table 3 andTau PET changes from baseline to week 78 seen in Table 4.

Safety: ARIA (Amyloid Related Imaging Abnormalities) was the most frequent adverse effect in ENGAGE and EMERGE study in terms of safety. ARIAs are aberrant findings in brain MRIs that can take the form of intracerebral bleeding, brain edema or sulcal effusions (ARIA-E), or both. These abnormal findings are frequently accompanied by superficial hemosiderin deposits (ARIA-H) [26]. Monitoring of safety included evaluation of vital signs, physical and neurological tests, reports of adverse events, including ARIA, and electrocardiography. Brain MRI scans were examined locally and by a central radiologist with experience in ARIA, along with hematologic and serum chemical testing, urine, and other tests[27]. In PRIME Study, ARIA was noted in the phase 1b trial of Aducanumab and has been linked to anti-Aβ antibody treatments[26]. In 2021, a safety study of these two trials (ENGAGE[22], EMERGE[23]) was published. ARIA-E (Amyloid Related Imaging Abnormalities due to Edema/Effusion), headache, nasopharyngitis, cranial micro hemorrhages (ARIA-H micro hemorrhage), fall, localized superficial siderosis (ARIA-H superficial siderosis), and lightheadedness were adverse events with an incidence >10% in any dose group[28]. Table 5 depicts the summary of safety of EMERGE and ENGAGE study. The incidence of ARIA-E was more common in high-dose group than in low-dose groups and greater in ApoE4 carrier levels than in non-carriers. In both trials, brain micro hemorrhages were the most common type of ARIA-H. ARIA-H is more common in patients who also have ARIA-E, according to this analysis (around about 40% of ARIA-E patients show evidence of ARIA-H). Finally, despite the high incidence, ARIA episodes typically resolve in 4-16 weeks, with less than 1% of patients receiving Aducanumab experiencing severe ARIA symptoms[26]. Table 6 summarizesadverse events which had an incident rate of over 10%

Clinical trials: This review included 10 studies of which six are phase I clinical trials, one of which is a phase II clinical trial, and three of which are phase III clinical trials. The majority of the included studies (n = 6) were conducted in the United States, one in Japan, and the remaining three in more than one country**.** Table 7 summarizes the clinical trials which were conducted to know the efficacy and safety profile of Aducanumab. PRIME TRIAL (NCT01677572): It was a multi-centric, double-blinded, three-masking (Participant, Care provider, Investigator), placebo-controlled trial. It was done to assess the pharmacokinetics, pharmacodynamic, safety, and tolerability data [29]. Aducanumab was given as a monthly intravenous infusion to 165 patients who had mild cognitive impairment and raised Aβ -amyloid plaques. In this trial, different doses of Aducanumab were given to see the effect of the drug to clear Aβ - amyloid plaque. PET (Positron Emission Tomography) scan was used to visualize amyloid plaque. It was quite evident that it shows treatment-dependent and dose-dependent clearance[37]. Better amyloid clearance is seen in patients who received the higher dose. Patients receiving higher doses with APO-E4 gene carriers showed Amyloid-related imaging abnormalities (ARIA) such as ARIA-E (edema) and ARIA-H (hemorrhage). Besides this, a phase 1b clinical trial was conducted to evaluate the ability of PET scans to detect -amyloid plaques. The study discovered that PET screening is a feasible and effective tool for identifying -amyloid plaques in Alzheimer's disease patients [38]. A phase 1 study (NCT01397539) was conducted in 2011 and ended in 2015. This USA-based. Placebo-controlled single ascending study was done to evaluate the safety and tolerability of Aducanumab doses administered as single intravenous (IV) infusions in participants with mild to moderate Alzheimer's disease. 53 patients participated in this study. Aducanumab was given at doses 0.3, 1, 3, 10, 20, 30, and 60 mg/kg. It evidenced a satisfactory safety and tolerability profile as well as a linear PK at doses of 30 mg/kg in this single-dose study [30]. Another phase 1 study (NCT02782975) was done in 2016 to see the pharmacokinetic data of the intravenous, subcutaneous route of Aducanumab. It was held between 28 healthy volunteers in the USA. The primary goals of this study were to compare the absolute bioavailability of Aducanumab from a single fixed subcutaneous (SC) dose to a single weight-based intravenous (IV) dose in healthy participants and to characterize the pharmacokinetics (PK) profile of Aducanumab. The secondary goals are to assess the safety and tolerability of Aducanumab administered via SC and IV routes in healthy volunteers, as well as to characterize additional PK parameters of a single, fixed SC dose of Aducanumab and a weight-based IV dose in healthy volunteers[31]. But the results are not published till now. PROPEL Study (NCT02434718): In the Japanese population, a phase 1 study was done to assess the effect of single and multiple ascending Doses of Aducanumab in Japanese participants with Alzheimer's disease. 21 Japanese patients with mild to moderate AD to evaluate safety, tolerability and pharmacokinetics. This study was completed but no data was posted[32]. A Study (NCT04924140) was done to assess the absolute bioavailability of Aducanumab in healthy volunteers. 30 healthy persons participated in this phase 1 trial.

The primary goal of this study is to compare the absolute bioavailability of Aducanumab from a single fixed subcutaneous (SC) dose to a single weight-based intravenous (IV) dose in healthy volunteers. The secondary goals of this study are to evaluate the safety and tolerability of Aducanumab administered SC in healthy volunteers, as well as to characterize additional pharmacokinetic parameters of a single, fixed SC dose of Aducanumab and a weight-based IV dose of Aducanumab in healthy volunteers[33]. This study also did not show any data. EVOLVE Study (NCT03639987): A phase II, multi-centered double-blinded study of Aducanumab was done in participants with mild cognitive impairment due to Alzheimer's disease or with mild Alzheimer's disease dementia to evaluate the safety of continued dosing in participants with asymptomatic amyloid-related imaging abnormalities [34]. This study aimed to characterize ARIA from both imaging and clinical standpoint, as well as the safety, tolerability, pharmacokinetics (PK), and immunogenicity of

Aducanumab. The study was halted due to the anticipated lack of efficacy of Aducanumab in the EMERGE and ENGAGE trials.

Two 18-month phase III trials (ENGAGE[21]and EMERGE [22]) were conducted to see if clearing -amyloid plaques affected delaying the progression of cognitive impairment in patients with mild cognitive impairment (MCI) and early dementia. Both trials included patients with ApoE4 gene carriers and non-carriers, with an average age of 70 years. The trial employed a clinical dementia rating scale to assess the effect of the drug on the progression of the disease. In March 2019, the ENGAGE and EMERGE trials were halted due to a lack of benefit based on data from the first 1748 patients but the trials were not called off due to safety concerns [39].But the reanalysis result surprised everyone as the study with 3285 patients study showed the beneficiary effect of Aducanumab in the Soluble amyloid-beta monomers with a higher dose in EMERGE trial [40]. Patients in the EMERGE trial who received high-dose Aducanumab improved by twenty-two percent in adjusted mean clinical dementia rating scores [41]. Not only is that but an eighty-four percent decline in caregiver's distress also seen. Furthermore, when compared to the placebo group, the ADCS-ADL scale and Neuropsychiatric assessment revealed a 40% reduction in functional decline. The NPI revealed an 87% reduction in behavioral changes from baseline scores, particularly in the EMERGE high-dose group. The ENGAGE trial, on the other hand, found no dose-dependent benefit of drug therapy over placebo [42].

Current ongoing confirmatory trial: Biogen is currently conducting two clinical studies named EMBARK and ICARE-AD. Patients who previously took part in Aducanumab studies (PRIME, EVOLVE, ENGAGE, and EMERGE) are enrolled in phase 3b, open-label EMBARK (NCT04241068). This study aims to evaluate Aducanumab's safety and effectiveness following an extended treatment gap [43, 44]. ICARE-AD is an observational study that was created after Aducanumab received approval (NCT05097131). It is a prospective cohort to gather information on safety and efficacy in clinical settings (Phase 4) [45, 46]. Moreover, Biogen is still developing ENVISION, a brand-new international, placebo-controlled clinical trial that is the FDA's needed phase 4 confirmatory study. The study is expected to be finished in 2026, and the business plans to begin patient recruitment in May 2022 [47, 48].

Approval of Aducanumab: Despite extensive scientific and clinical research, as well as the availability of several authorized medications, there is still a great unmet medical need for effective Alzheimer's disease treatment, particularly for those that aim to address the biological causes of the disease to modify it in a positive way over the long term. So, the invention of Aducanumab shows a new ray of hope for Alzheimer's patients. But its approval is quite controversial. Due to close coordination between the sponsor (Biogen) and the FDA during the entire process, Aducanumab's journey to approval was a little unusual [49]. Figure2 briefly illustrates the events occurred during the approval of Aducanumab

FDA approval: The Peripheral and Central Nervous System (PCNS) Medicines Advisory Committee convened on November 6, 2020 to analyze Aducanumab's clinical data. Ten members voted against the approval of Aducanumab but one-member abstained. They believed that the study findings were contradictory and that the data did not provide enough proof of therapeutic efficacy [23, 27]. Three members of the PCNS committee resigned as a result of the FDA's accelerated approval of Aducanumab on June 7, 2021, which was against the independent committee's recommendation[50]. Patients can gain early access to medications that treat critical diseases and significantly improve existing medications thanks to the accelerated approval procedure. Instead of clinical results, a surrogate endpoint that is expected to predict clinical benefit served as the foundation for this approval [51].

EMA Decision: Aducanumab has been up for assessment at the European Medicine Agency (EMA) in Europe since October 2020 [52]. The marketing application for Aducanumab was rejected by the Committee for Medicinal Products for Human Use of the EMA on December 17, 2021 [53, 54]. EMA specialists believed that this medicine did not demonstrate a clear efficacy signal or a suitable safety profile to treat patients in the early stage of AD based on the studies that were conducted.

Controversy: Following the FDA's approval of Aducanumab, a number of professionals voiced their disapproval of the decision [55]. (a) The main focus of the argument is the inconsistent findings of phase 3 trials. Available data are insufficient to substantiate the clinical efficacy of Aducanumab[56]. (b) Most experts agree that Aβ plaques are not a reliable surrogate endpoint because there is no evidence that Aβ decrease correlates with clinical benefits [57]. Furthermore, more recent research revealed that tau accumulation rather than Aβ had a stronger correlation with cognitive impairment [58]. (c) The FDA and sponsor collaborated together, which may have compromised the FDA's decision-making objectivity. Also, the AD advocacy groups put a lot of pressure on the FDA, arguing that even a little advantage of Aducanumab would be helpful to patients and caregivers [59]. (d) The approval of Aducanumab could hinder scientific progress by forcing pharmaceutical companies to focus only on amyloid pathology and forsake other AD-related objectives in favor of gaining clearance for an unproven biomarker[60]. These points create a lot of controversy about Aducanumab's approval. Therefore, a use guideline for Aducanumab was prepared by an expert panel to address these important concerns and direct medical professionals.

Approved dosage and recommendations: Clinicians need direction on how to apply this novel therapy properly. For this a study regarding appropriate dosing recommendations for Aducanumab was done by J. Cummings, P. Aisen et al and an expert panel was formed. The conduct of Aducanumab's pivotal studies, the updated Prescribing Information and the opinions of an expert panel were used to create the appropriate use recommendations. According to the expert panel, those who have been diagnosed with MCI and moderate AD should take Aducanumab. A score of less than 21 on the MMSE (or a comparable cognitive test) and a positive amyloid PET or CSF biomarker consistent with AD are also essential requirements for starting treatment [61]. This study recommended performing MRI before the fifth, seventh, ninth, and twelfth infusions to improve detection since the majority of ARIA happen during the titration period of Aducanumab.

They also recommend additional criteria for stopping treatment if ARIA becomes severe or recurrent. Following a preliminary titration, 10 mg/kg of Aducanumab is the suggested dosage. Every four weeks, at least twenty-one days apart, an intravenous (IV) infusion of Aducanumab is administered over the course of 45-60 minutes [61]. Table 8 shows the FDA approved dosing schedule of Aducanumab.

Cost of treatment: As Aducanumab is a monoclonal antibody, it is quite obvious that it would be more costly than the standard of care. Aducanumab costs $56,000 per year (range: $33,600-84,000). A 5-year cohort study of persons aged 65 years with mild Alzheimer's disease was done to analyze the cost-effectiveness of Aducanumab and it found that it is not at all cost-effective in its ideal situation that it completely delays the progression of the disease [62]. Many insurance companies and hospitals refused to pay for the treatment because of its doubtful efficacy and the initial cost of US$56,000. Due to the limited patient access to Aducanumab in the first six months, Biogen saw unsatisfactory sales. Following the EMA's denial, Biogen announces a price cut of $28,200 at the start of 2022 in an effort to promote patient access to Aducanumab by expanding insurance coverage [63].

Future prospective: The approval of Aducanumab will significantly affect the treatment of AD. Passive immunotherapy, vaccinations, and early detection using neuro-imaging, CSF and plasma biomarkers are anticipated to be the mainstays of AD management in the future. The major disease diagnostic criteria have been AD CSF biomarkers. Recent advancements in mass spectrometry and ultrasensitive immunoassays have made it possible to measure plasma biomarkers for amyloid plaque formation and neurodegeneration (tau and neuro-filament light proteins) [64]. Besides Aβ amyloid, various biomarkers like p-Tau217 and p-Tau181 have the potential to differentiate Alzheimer's from another neurodegenerative disease. Numerous anti-amyloid beta and anti-tau treatments (Lecanemab, Donanemab, Crenezumab) have been studied or are being studied right now [65-67].

CONCLUSION

Researchers have come to the conclusion that the proteins tau and Aβ have antagonistic roles in the neurodegenerative process 19. The normal progression of AD may be altered by a combination therapy that targets the accumulation of Aβ aggregates and hyperphosphorylated intracellular tau proteins[68]. That's why combinational therapy becomes the need of the hour[69]. Alzheimer's disease has a new therapy called Aducanumab. This monoclonal antibody has specificity for Aβ amyloid aggregates. Aducanumab was the first medication under the accelerated approval pathway to be approved by the US Food and Drug Administration (FDA) and address the patho-physiology of Alzheimer's disease in June 2021. It gives both chances and difficulties for its inclusion in the management of AD patients. In patients with early-onset Alzheimer's, Aducanumab has the potential to decrease the cognitive deterioration associated with the illness. Aducanumab does not, however, arrest memory decline. Its unsatisfactory results from various clinical trial and accelerated FDA approval create a lot of chaos regarding the acceptability and beneficiary effect of Aducanumab among patients. Irrespective of debate, it is undeniable that Aducanumab greatly lowers brain levels of Aβ, a symptom of AD. The findings also demonstrated that Aducanumab reduces the amount of tau in the brain, the second hallmark of AD. This observation may mark a turning point in the treatment of Alzheimer's disease.

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